Wilson's disease:

aspects of diagnosis and treatment

Presentation by Rupert Purchase

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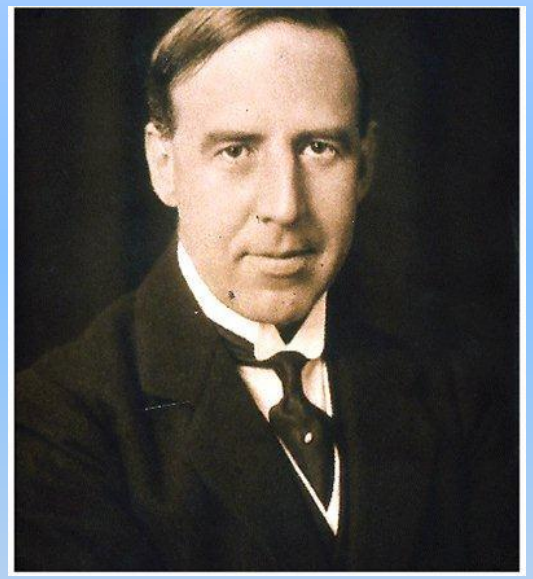
Wilson's disease

1. An hereditary disease of (dietary) copper overload. Fatal if left untreated.
2. Associated with reduced excretion of copper in bile.
3. In individuals ranging from age three years to over 50 years.
4. Symptoms vary among and within families.
5. Treatment for copper overload is life-long.

2012 − centenary of the first publication on Wilson's disease



BRAIN. [MARCH, 1912.]

PART IV., VOL. 34.

Original Articles and Clinical Cases.

PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.

Registrar to the National Hospital, Queen Square, London.

(From the Laboratory of the National Hospital, Queen Square.)

Samuel Alexander Kinnier Wilson (1878-1937)

Two patients (S.T. & E.P.) with Wilson's disease (pre-symptomatic) described in *Brain* 1912

FIG. 12.—Photograph of S. T. before the onset of the symptoms of progressive lenticular degeneration.

FIG. 20.—E. P. in his school days.

S.T. & E.P showing symptoms of neurological Wilson's disease

Figure 1 Photograph of S.T. taken at Virginia Water. Characteristic appearance of face and upper limbs. (For this photograph I am indebted to Dr. G. W. Smith).

Figure 3 E.P. (June 4, 1910). Note vacant expression, open mouth, sialorrhoea, contractures. (Exposure 1/250s, to counteract effect of constant tremor).

Clinical manifestations of Wilson's disease

Hepatic

- Persistently elevated serum aminotransferases
- Chronic hepatitis
- Cirrhosis (decompensated or compensated)
- Fulminant hepatic failure (+/- haemolytic anaemia)

Clinical manifestations of Wilson's disease

Neurological

- Tremor
- Choreiform movements
- Parkinsonism or akinetic rigid syndrome
- Gait disturbances
- Dysarthria
- Pseudobulbar palsy
- Rigid dystonia
- Seizures
- Migraine headaches
- Insomnia

Clinical manifestations of Wilson's disease

Ophthalmic

- Kayser-Fleischer rings
- Sunflower cataracts

Psychiatric

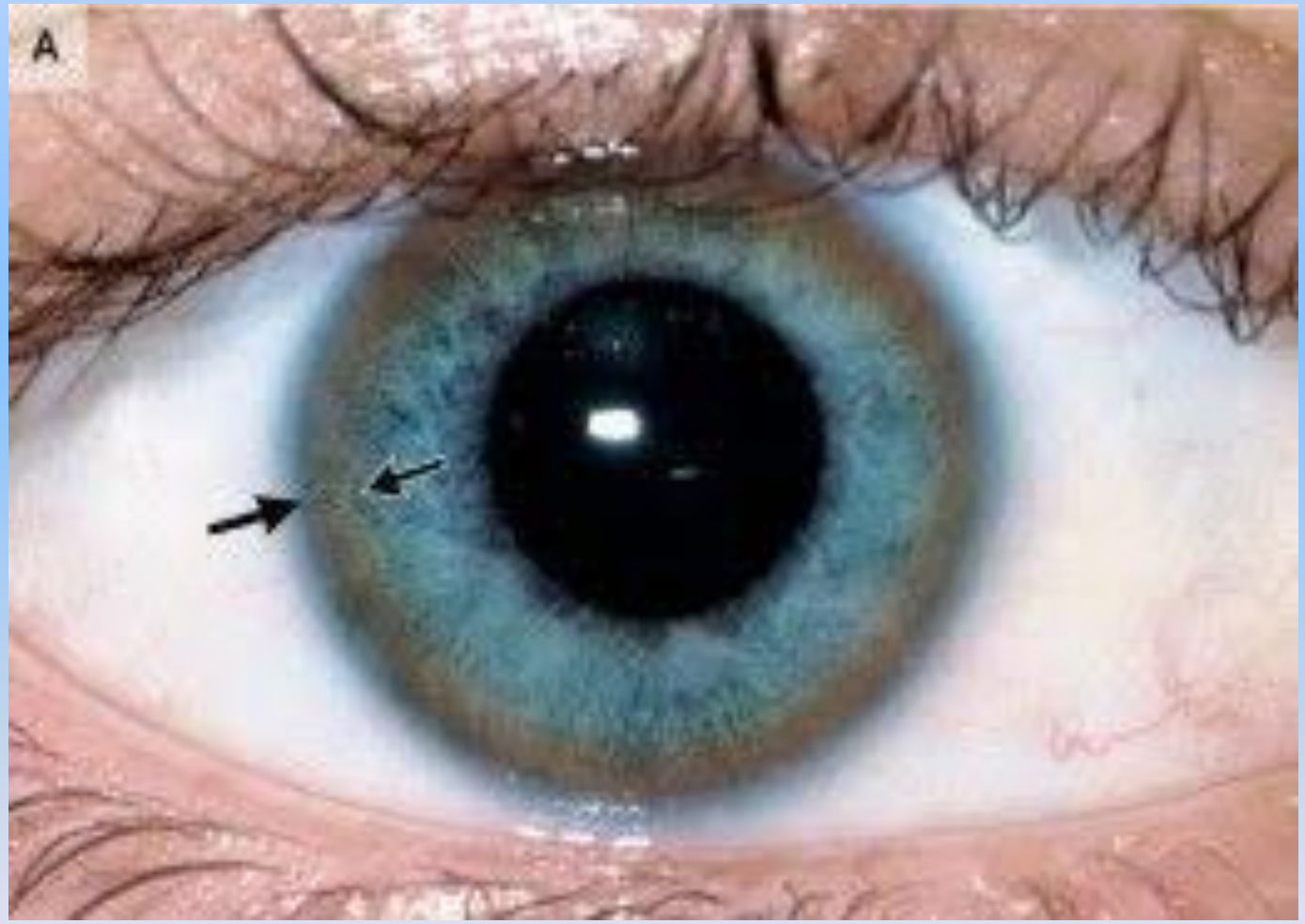
- Depression
- Neuroses
- Personality changes
- Psychosis

Lancet, 2007, **369**, 397-408

Diagnostic tests for Wilson's disease

- Opthalmic slit lamp examination for Kayser-Fleischer rings
- Serum caeruloplasmin test
- 24-hour urine copper test
- Liver biopsy for histology and histochemistry and copper quantification
- Genetic testing, haplotype analysis for siblings and mutation analysis
- Brain MRI scan

Kayser-Fleischer ring



18-year old female WD patient before chelation therapy

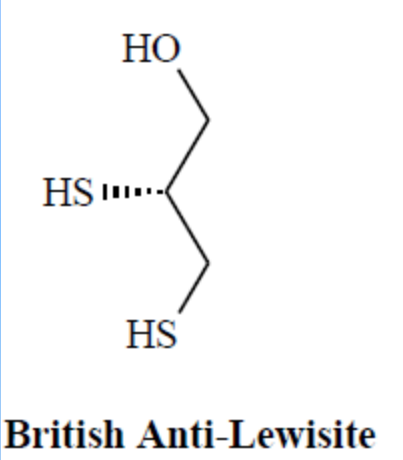
New Engl. J. Med., 2012. **366**; e18

Treatment options for Wilson's disease

Reduction in copper overload:

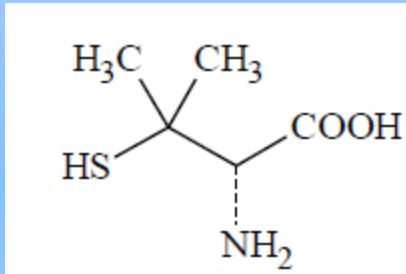
- Chelation therapy
- Zinc salts
- Tetrathiomolybdate
- [Liver transplant]

Three copper chelating agents used to treat Wilson's disease



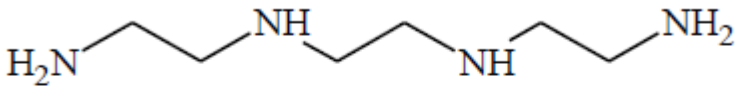
British Anti-Lewisite

J.N. Cumings,1951 (intramuscular)



D-Penicillamine
(3-Mercapto-D-valine)

J.M. Walshe, 1956 (oral)



Trientine
(Triethylenetetramine; *N*,*N*′-Bis(2-aminoethyl)-1,2-ethanediamine)
Clinically, the dihydrochloride is administered.

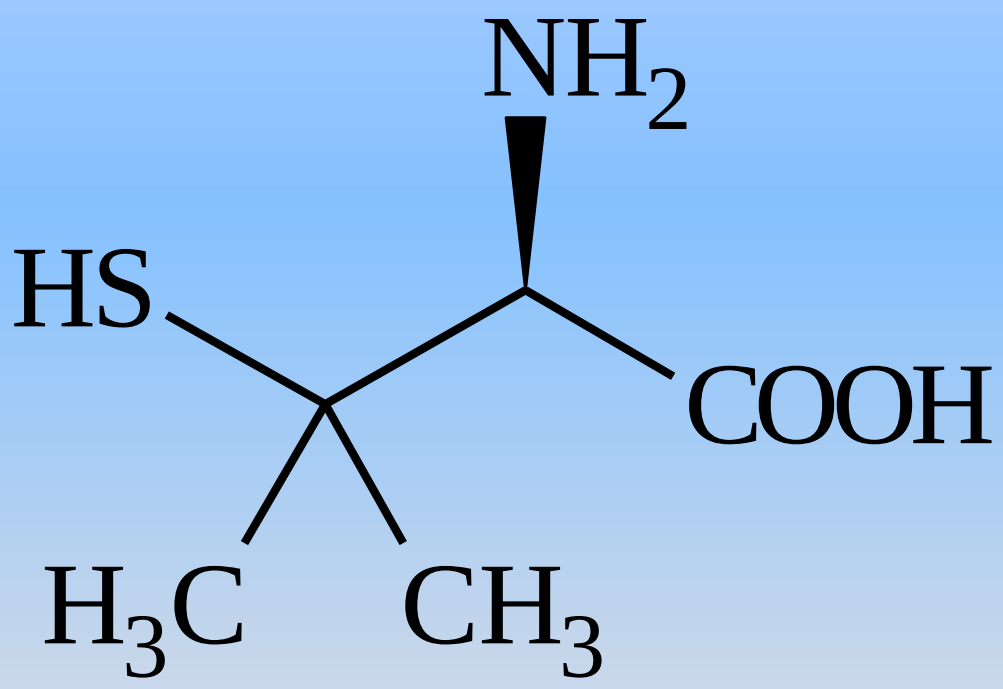
J.M. Walshe, 1969 (oral)

Other (oral) drugs used to treat Wilson's disease

- Zinc acetate (Wilzin®) or zinc sulfate (G. Schouwink, 1961)
- Ammonium tetrathiomolybdate and bis(choline) tetrathiomolybdate (TTM)
- TTM used to treat neurological Wilson's disease

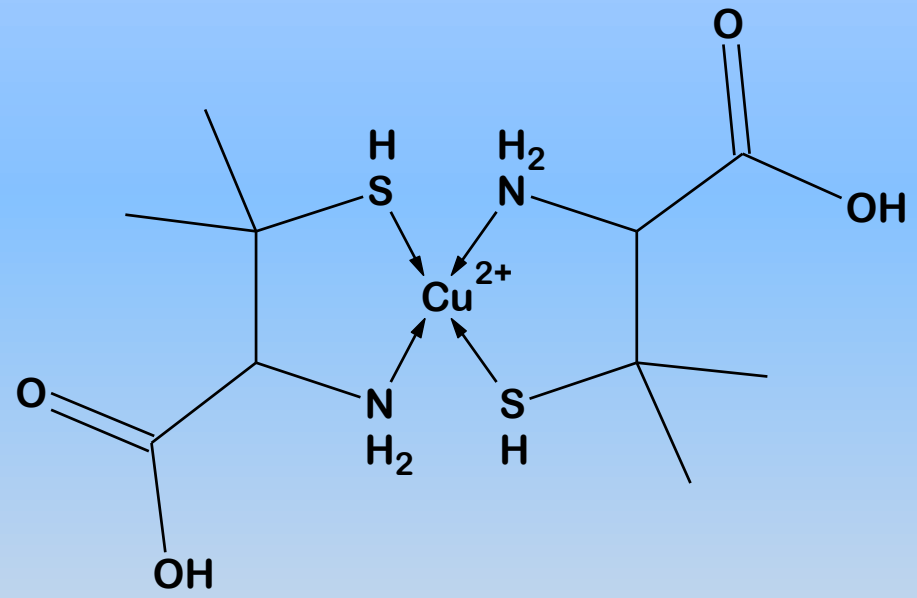
D-Penicillamine

A monodentate, bidentate or a tridentate ligand



Initial dose 1000–1500 mg per day in two to four divided doses

Putative copper-penicillamine complex ion



Because: $2RSH + 2Cu^{2+} \longrightarrow R–S–S–R + 2Cu^{+} + 2H^{+}$

D-Penicillamine and Cu^{2+} – aqueous chemistry

- ‘Reductive chelation’
- Form a purple mixed valence cluster complex $[Cu(II)_6Cu(I)_8Pen_{12}Cl]^{5-}$
- Relevance to therapeutic action?

Therapeutic action of D-penicillamine

- Induces cupruresis
- Reduces Cu(II) to Cu(I)
- Forms cuprous–penicillamine complexes, whose structures are pH dependent
- Does not mobilise Cu(II) bound to albumin; acts on other copper pools *in vivo*
- Its enhanced cupruretic properties are still not understood? Particularly in long-term use.

D-penicillamine – adverse reactions

10-20% of patients develop immunologically induced intolerance to penicillamine

Most serious:

- Immune-complex nephritis
- Systemic lupus erythematosus (SLE)
- Haemolytic anaemia
- Symptoms mimicking Goodpasture's syndrome

Also, direct chemical toxicity, e.g. pyridoxine deficiency and dermatopathy

J. M. Walshe, *The Lancet*, March 20, 1982, 643

D-penicillamine – adverse reactions

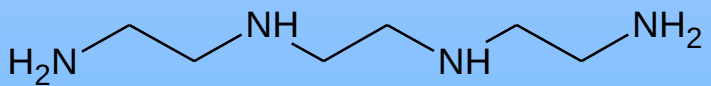
Neurological worsening:

"*No new patient should be prescribed penicillamine* de novo *and sent home. The first 2 weeks are critical for that small, but unpredictable number of patients who may undergo rapid deterioration* …"

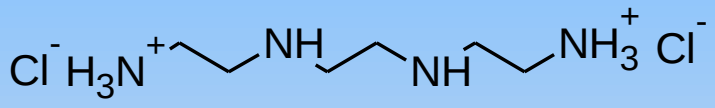
John Walshe, *Curr. Treat. Options Gastroenterol.*, 2005, **8**, 467

Triethylenetetramine (trientine) and its synonyms

$H_2NCH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$



Triethylenetetramine



Triethylenetetramine dihydrochloride

Synonyms:
Trientine dihydrochloride, BAN, INN
Trientine hydrochloride, USAN
Trien; TRIEN; TETA; Cuprid (Merck); Syprine (Merck);
Metalite (Tsumura); Laszarin (Protemix); MK 681; PX 811019 (Protemix)

“Drugs for Rare Diseases”

“…Recently the hospital pharmacy [Addenbrooke’s] agreed to take over the purification of trien.2HCl [trientine]…In my view this do-it-yourself exercise has continued quite long enough and should be placed on a sound commercial basis.”

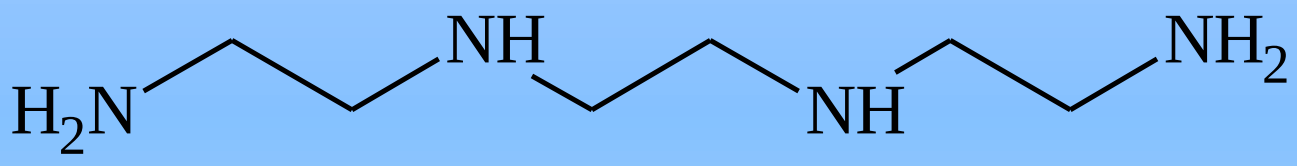
Dr John Walshe, *Brit. Med. J.*, 20th September 1975, p 701. Reported in *New Scientist*, 25th September, 1975

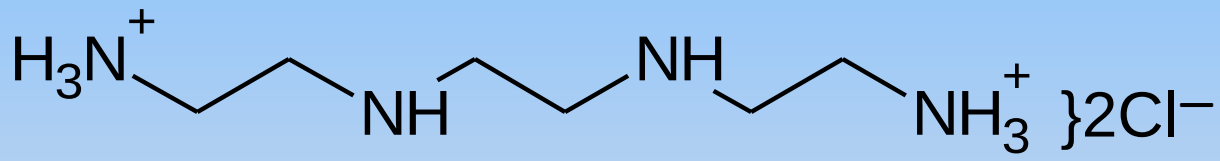
Production of trientine dihydrochloride

- From commercial (technical grade) triethylenetetramine
- A very cheap industrial chemical (£20/kilogram: Aldrich catalogue)
- Trientine – UK price (1 x 300 mg capsule) *ca.* £30
- Trientine – USA price (1 x 250 mg capsule) *ca.* £140

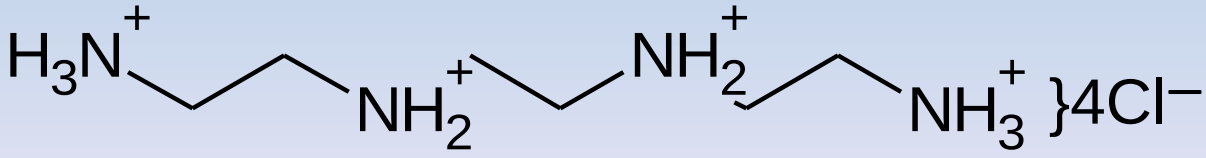
Trientine

A quadridentate ligand



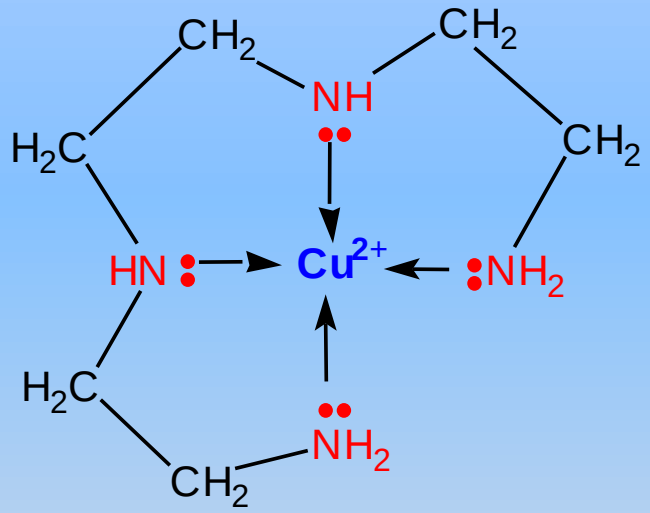


Dihydrochloride



Tetrahydrochloride

Coordination of trientine with cupric ions



$Cu^{2+} + \text{trien} \leftrightarrows [Cu(\text{trien})]^{2+}$

Stability constant (K_{ML})

$K_{ML} = [Cu(\text{trien})]^{2+}/[Cu^{2+}][\text{trien}] = 10^{20.1}\ \text{mol}^{-1}\ \text{dm}^3$

$\log_{10} K_{ML} = 20.1$ (a typical experimental value).

Action of trientine

- Induces cupruresis
- Chelates copper in the intestinal tract, reducing copper absorption *in vivo*
- Removes Cu(II) from Cu(II)–albumin to form $[Cu(trien)]^{2+}$

Administration of trientine.2HCl

- Initial dose of **trientine** 750–1500 mg/day in two or three divided doses

- Given on an empty stomach – 1 hour before or 2 hours after a meal

A patient showing improvement in the symptoms of neurological Wilson's disease following treatment with trientine

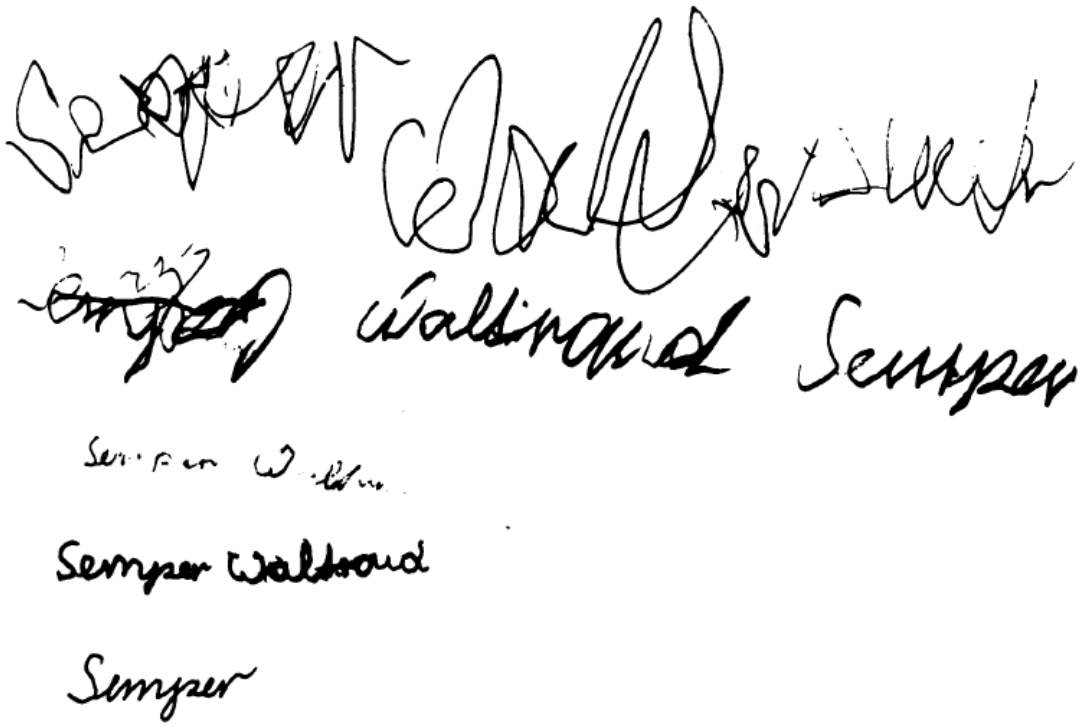


Fig 1 *Improvement in patient's handwriting from October 1975 to April 1976 during treatment with TETA.* (*Reduced to half scale*)

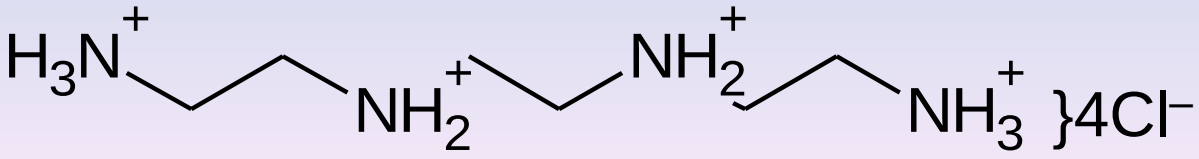
Harders, H.; Cohnen, E., *Proc. R. Soc. Med.*, 1977, 70 Suppl. 3, 10

Trientine – adverse effects

- Sideroblastic anemia (RARE)
- Lupus-like reactions (from residual D-pen treatment?) (RARE)
- Haemorrhagic gastritis, loss of taste, and skin changes (rashes) (RARE)
- Trientine-induced colitis (RARE)
- Neurological deterioration during trientine treatment has been reported

Trientine tetrahydrochloride (Cuprior)

- Manufactured in tablet form in France
- EMA approval (2017) for treating Wilson's disease in EU
- Tablets stable at room temperature
- Claimed to be effective at a lower equivalent dose than the dihydrochloride



Zinc salts

- Zn^{2+} induces intestinal metallothionein, which preferentially binds to copper within the duodenal enterocyte
- Copper absorption into the circulation is reduced, and copper is lost when the enterocyte is shed during normal cell turnover
- Without normal absorption but with continuing copper losses there is a negative copper balance

Treatment of Wilson's disease with zinc salts

- Recommended as a maintenance therapy after initial 'decoppering'
- Used in asymptomatic or presymptomatic family members of individuals with Wilson's disease
- Dyspepsia a side-effect

Zinc acetate crystals

Tetrathiomolybdate (TTM) MoS_4^{2-}

- Ammonium tetrathiomolybdate $(NH_4)MoS_4$

  (J.M.Walshe, 1984; G.J. Brewer, 1991)

- Bis(choline) tetrathiomolybdate

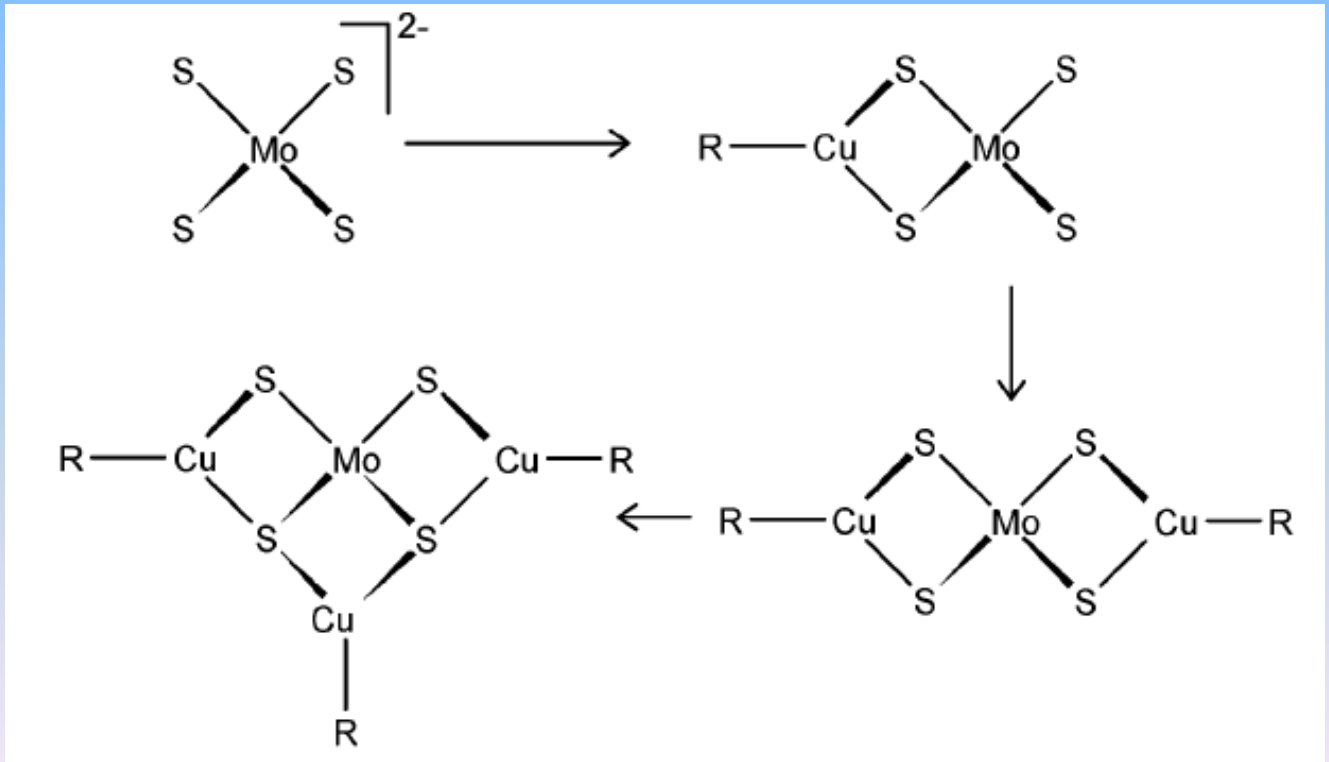
Code Name WTX101 (Wilson Therapeutics)

WILSON THERAPEUTICS

ALEXION

Tetrathiomolybdate (TTM) MoS_4^{2-}

TTM interacts with Cu(I) to form copper–molybdenum–sulfur clusters:



Action of TTM

- Decreases absorption of dietary copper
- Augments Cu excretion into bile
- WTX101 undergoing clinical trials in the UK
- Phase 2 published; Phase 3 in progress

The Lancet Gastroenterology & Hepatology, 2017. **2**, 869-876

Wilson's disease – genetic aspects

- Characterized by decreased biliary excretion of copper and reduced incorporation of copper into apoceruloplasmin
- Caused by homozygous or compound heterozygous mutations in the *ATP7B* gene, which encodes a copper-transporting P-type ATPase
- Over 500 mutations in the *ATP7B* gene have been reported
- Accepted prevalence of WD of 1:30 000 questioned by Sheffield Diagnostic Genetics Service
- Possibility of many undiagnosed WD cases in the UK

Brain, 2013, **136**, 1476-1487

Wilson's Disease Support Group – UK (WDSG – UK)

- Provides support for patients, families, and friends
- Raises funds and sponsors research into Wilson's disease
- Annual newsletter
- WDSG – UK website & Facebook page

Wilson's

Wilson's Disease Support Group – UK

www.wilsonsdisease.org.uk

UK WD patients' concerns

- Awareness of WD by health professionals; delayed initial diagnosis; unrecognised cases
- Access to WD specialists — WD specialists located in centres of excellence in the UK; a holistic approach to treatment
- More attention to post-diagnosis 'quality of life' issues:
  - effect of medication on skin;
  - problems with joints;
  - appreciation of residual psychiatric problems
- Issues with prescription charges — simplification of any available reductions in prescription costs

Wilson's Disease Support Group – UK Meeting, King's College Cambridge, 2006

Dr John Walshe and his first WD patient from 1955 (2017 WDSG-UK Annual Meeting)

BASL Wilson's Disease Special Interest Group

- WD Special Interest Group comprises UK clinical and laboratory specialists
- Aims are to foster collaboration for clinical and scientific research
- Provide a forum to discuss and disseminate best practice
- Act as a stimulus towards Centres of Excellence for Wilson's disease

BASL
British Association for the Study of the Liver

WILSON DISEASE

PATHOGENESIS, MOLECULAR MECHANISMS, DIAGNOSIS, TREATMENT AND MONITORING

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